Evaluation of the Bioavailability of Sarpicillin, the Methoxymethyl Ester of Hetacillin, in Humans

S. STAVCHANSKY *x, R. S. PEARLMAN *, D. R. VAN HARKEN ‡, R. D. SMYTH ‡, G. H. HOTTENDORF ‡, A. MARTIN *, J. NEWBURGER *, and L. W. SCHNEIDER *

Received March 15, 1982, from *The University of Texas at Austin, College of Pharmacy, Drug Dynamics Institute, Austin, TX 78712, and ‡Bristol Laboratories, Syracuse, NY 13201. Accepted for publication December 21, 1982.

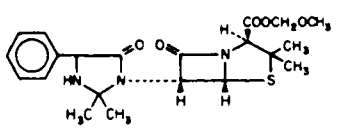
Abstract □ The relative bioavailability of sarpicillin (the methoxymethyl ester of hetacillin) from three different oral dosage forms was compared in humans employing a three-way crossover study design. Each unit dose contained 250 mg of sarpicillin in terms of anhydrous ampicillin activity. The comparative bioavailability of a tablet containing added buffer, a liquid-filled capsule, and a standard powder-filled capsule was determined. The bioavailability parameters were C_{max}, t_{max}, and AUC of intact plasma sarpicillin levels and saliva ampicillin levels. Significant correlation was found between plasma sarpicillin levels and saliva ampicillin levels following the administration of sarpicillin. All three formulations yielded statistically similar C_{max} and AUC values with respect to plasma sarpicillin and saliva ampicillin levels. However, a more rapid absorption of intact sarpicillin was observed with the buffered tablet formulation, as reflected by significantly smaller t_{max} for both plasma sarpicillin and saliva ampicillin levels. The faster absorption from the tablet formulation gave more precise absorption among subjects.

Keyphrases □ Sarpicillin—evaluation of bioavailability, humans, methoxymethyl ester of hetacillin □ Bioavailability—sarpicillin, methoxymethyl ester of hetacillin, humans □ Hetacillin—methoxymethyl ester, evaluation of bioavailability of sarpicillin in humans

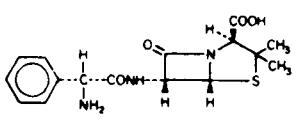
Ampicillin (II) is an acid-resistant form of penicillin, whose oral absorption is incomplete and erratic in humans. Factors which have been shown to account for differences in ampicillin bioavailability are intersubject variability (1), age of subjects (2), liver disease (3), and variation in forms [hydrate (4) and salt (5)] of ampicillin. Esters of penicillin, such as pivampicillin hydrochloride and hetacillin have been introduced in an effort to improve the properties of ampicillin. Hetacillin is susceptible to rapid hydrolysis both *in vivo* and *in vitro* (6, 7). However, this drug improves ampicillin bioavailability (8), and its activity depends on the formation of ampicillin.

Sarpicillin free base [methoxymethyl (2*S*,5*R*,6*R*)-6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (I) a new semisynthetic penicillin derivative, the methoxymethyl ester of hetacillin is a basic, nonionizable, highly lipophilic antibiotic possessing the same antimicrobial spectrum and activity as ampicillin. It is effective against Gram-negative pathogens such as *Hemophilus influenzae* and the coliform group. The chemical relationship of sarpicillin to ampicillin is apparent.

Distribution of antibiotics to tissues is of increasing clinical concern (9, 10). Sarpicillin is of particular importance because it results in high tissue concentrations of ampicillin, particularly in lipid-rich regions such as the brain and prostatic tissue, as well as in the CSF and lungs.



I



II

High concentrations of ampicillin are also observed in red blood cells following the administration of sarpicillin (11–14). Sarpicillin administered orally in a single dose appears to have advantages such as more rapid absorption, higher and earlier plasma levels, and a larger volume of distribution when compared with ampicillin (15). The objective of the present investigation was to prepare a formulation of sarpicillin base which would provide better systemic ampicillin levels compared with an equivalent dose of pure ampicillin and would protect sarpicillin from possible hydrolysis in the GI tract. Human plasma, saliva, and urine levels of sarpicillin in terms of ampicillin activity of three different formulations are presented.

EXPERIMENTAL

Study Design—Six normal healthy male volunteers, 20–35 years old, were selected for participation in the study. The range in subject weight did not exceed 30 kg.

Within 1 week preceding the study, subjects were given a thorough physical examination, and the following clinical laboratory tests were performed: (*a*) hematology: hemoglobin, hematocrit, sedimentation rate, white blood cell count, platelet estimate, and differential, (*b*) blood chemistry: SMA 12/60 analysis or equivalent, and (*c*) urinalysis: physical characteristics, albumin, sugar, and microscopic examination. Subjects whose values for any of the laboratory tests were outside of the normal range were excluded from the study.

Subjects were excluded from the study who: (*a*) had received any drugs, with the exception of moderate use of alcohol and tobacco, for a period of at least 2 weeks prior to the study; (*b*) showed significant physical or organ abnormality or disease; (*c*) required maintenance therapy with any drug or history of drug dependency; (*d*) had any recognizable surgical disease; (*e*) had a history of hypersensitivity to any antimicrobial agents

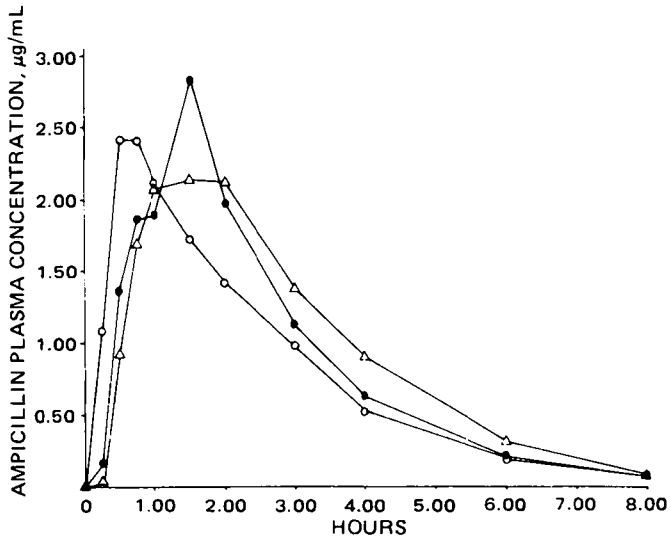


Figure 1—*Ampicillin plasma concentration obtained after single oral administration of treatments A, buffered tablet (○), B, soft gelatin capsule (●), and C, standard gelatin capsule (△).*

0022-3549/84/0200-0169$01.00/0

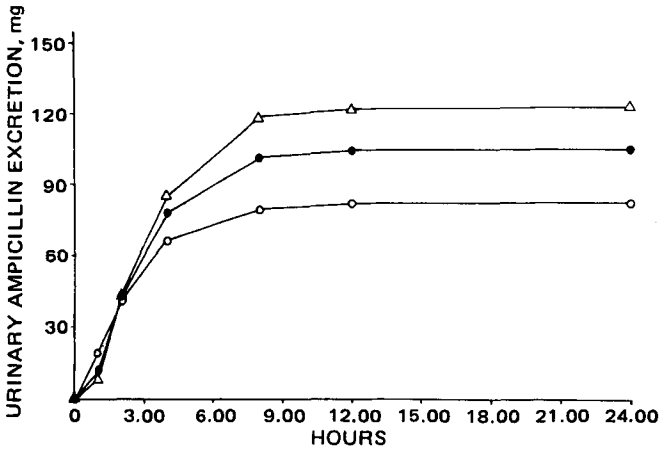


Figure 2—*Urinary ampicillin excretion after single oral administration of treatments A, buffered tablet (○), B, soft gelatin capsule (●), and C, standard gelatin capsule (△).*

or other allergens (pollens, *etc.*), previous use of any cardiac glycoside, any type of anemia, cardiac or respiratory diseases, renal or liver impairment, thyroid disease, recent GI or glucose-6-phosphate dehydrogenase deficiency. Informed consent was obtained from the subjects.

During the study day a physician was present, and all subjects were confined in the clinical facilities at the University of Texas Health Science Center at San Antonio. Subjects were fasted from midnight prior to the drug administration, and each subject drank at least 500 mL of fluids during the evening preceding the study day. No alcoholic beverages were allowed between supper and midnight. On the day of the study, no beverages were permitted during the fasting period. Following 4-h postdose fasting, the subjects were allowed to eat and drink a specific diet.

All subjects were given 200 mL of water at the start of the treatment, regardless of dosage administered. An additional 200 mL of water was given every 2 h after treatment while the fasting was still being maintained. After drug administration, the subjects were ambulatory throughout the test day, and proceeded with normal daily routine while being available for blood, saliva, and urine sampling.

The experimental design in the present study is an exact balance of formulations over weeks, and each subject received every formulation. The design was repeated twice for a total of two Latin squares. Each subject received single 250-mg oral doses of sarpicillin base on each of 3 study days.

Study days were separated by 1-week washout periods to allow for drug elimination as well as to allow for stabilization for the blood volumes of the subjects. Treatments A, B, and C consisted of a buffered tablet, a soft gelatin capsule, and a standard gelatin capsule, respectively. Each formulation contained 250 mg of sarpicillin base in terms of ampicillin activity[1].

Blood samples were drawn by serial venipuncture at time zero (prior to drug administration) and at 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, and 8 h after drug administration. All blood specimens were collected in heparinized tubes[2]. The heparinized tubes were gently inverted a few times to allow for complete mixing, cooled in ice for 3–5 min, and then centrifuged at 4500 rpm for 5 min in a refrigerated centrifuge. The plasma was transferred into polypropylene tubes, immediately flash frozen by immersion in an ethanol–dry ice bath, and was then kept frozen until assayed.

Urine specimens were collected at time zero (prior to drug administration). Saliva samples (~3–5 mL) were collected at time zero and at 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, and 8 h after drug administration. Saliva production was induced by instructing the subject to roll a glass marble in his mouth for 3–5 min prior to the collection period and then to expectorate into a plastic container. Each saliva sample was immediately frozen by immersion in an ethanol–dry ice bath and was kept frozen until assayed.

Analytical Methodology—Bioassays for antibiotic activity were performed by standard microbiological agar-diffusion assay methodology (16). Sarpicillin was determined by extracting the biological sample with chloroform after the addition of an equal volume of 0.1 M phosphate buffer, pH 7.4. The ampicillin remained in the aqueous phase. Antibiotic activity in each phase was quantitated by the disk-plate assay using

[1] Supplied by Bristol Laboratories, Syracuse, NY 13201.
[2] Becton, Dickinson, Rutherford, NJ 07070.

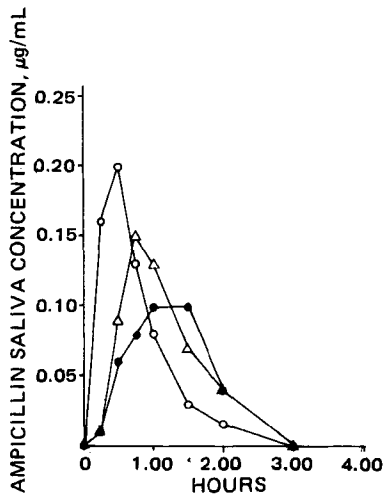


Figure 3—*Ampicillin saliva concentration obtained after single oral administration of treatments A, buffered tablet (○), B, soft gelatin capsule (●), and C, standard gelatin capsule (△).*

Sarcinea lutea ATCC 9341 as the assay organism. Ampicillin trihydrate and sarpicillin hydrochloride were used as the reference standards. Chloroform did not interfere with the assay.

Ampicillin trihydrate standards were prepared in distilled water, and sarpicillin base standards were prepared in chloroform. Standard solutions (1 mg/mL) were prepared for both compounds based on ampicillin potency. Two milliliters of each stock solution was diluted to 100 ml using the appropriate diluents. From this diluted standard, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 9.0 mL were placed in 100-mL volumetric flasks and diluted to volume. These dilutions yielded 1–9 ng of ampicillin activity when 5 μL of each standard solution was spotted on opposite site disks in duplicate. When completed, each dish was covered with cardboard, marked, and stored at 4°C until all samples were spotted.

Plasma, saliva, and urine samples were made for each dilution so that an average diameter value could be obtained. When the spotting of all samples was completed, the samples and standard dishes were placed in an incubator at 28°C overnight. Zone diameters for the various diluted samples were averaged and the concentrations determined from the appropriate standard curve.

RESULTS

Ampicillin—Average ampicillin plasma, saliva, and urine data obtained after oral administration of a buffered tablet, a liquid formulation in a soft gelatin capsule, and a standard gelatin capsule (treatments A, B, and C) containing 250 mg of sarpicillin base in terms of ampicillin activity are illustrated in Figs. 1–3, respectively. The data obtained represent unchanged ampicillin.

The average ampicillin level *versus* time curves (Fig. 1) for treatments A, B, and C were fitted to Eq. 1 (17) using the digital computer program NONLIN (18):

$$C_p = \frac{k_a \cdot D}{(k_a - K)Vd}\{e^{-K(t-L)} - e^{-k_a(t-L)}\} \qquad \text{(Eq. 1)}$$

where k_a is the first-order absorption rate constant, K is the overall first-order elimination rate constant, D represents the absorbed dose, Vd is the volume of distribution, C_p represents ampicillin plasma concentration, and L is the lag time for absorption. The parameters of the computer fit are K, k_a, D/Vd, and L. Based on R-squared values, slightly better fits were obtained when weights of $1/y_{obs}$ were used rather than weights of one. The results for the three treatments are summarized in Table I.

Based on the computer-generated parameters K, k_a, L, and D/Vd for ampicillin plasma data, estimates of the time to peak (t_{max}) peak concentration (C_{max}), and area under the curve (AUC) were calculated:

$$t_{max} = L + \frac{\ln (K/k_a)}{K - k_a} \qquad \text{(Eq. 2)}$$

$$C_{max} = \frac{k_a D}{(k_a - k)Vd}\{e^{-K(t_{max}-L)} - e^{-k_a(t_{max}-L)}\} \qquad \text{(Eq. 3)}$$

$$AUC = D/K \cdot Vd \qquad \text{(Eq. 4)}$$

Table I—Pharmacokinetic Parameters of Ampicillin After Administration of Sarpicillin

Parameter[a]	Treatment[b] A	B	C
K, h^{-1}	0.464 (0.016)	0.590 (0.068)	0.555 (0.061)
K^c, h^{-1}	0.453	0.441	0.507
k_a, h^{-1} [d]	6.958 (1.337)	1.528 (0.267)	1.320 (0.259)
L, h	0.184 (0.013)	0.221 (0.008)	0.295 (0.036)
D/V μg/mL	2.998 (0.081)	4.006 (0.438)	4.224 (0.454)
CL_R, L/h[e]	10.76	12.43	16.02

[a] See text for parameter definitions. Calculated from the NONLIN digital computer fit of average plasma ampicillin levels. Weights = $1/y_{obs}$ for treatment A (buffered tablet), treatment B (soft gelatin capsule), and treatment C (standard gelatin capsule). [b] *SD* in parentheses. [c] Values obtained from sigma-minus plots of urine data. [d] Paired t test at $p < 0.05$ indicates a significant difference between treatments A–B and A–C. [e] Values obtained from overall renal clearance plots.

The average of the observed values of t_{max}, C_{max}, and AUC for the individual ampicillin level *versus* time curves are listed in Table II along with the results of analysis of variance (ANOVA) and paired t tests.

The amount of ampicillin remaining to be excreted in the urine ($U_\infty - U_t$) was calculated and plotted *versus* time on a semilogarithmic scale (19). For these sigma-minus plots, the value of U_∞ was taken as the amount of ampicillin excreted in the urine after 24 h. Least-squares linear regression was used to determine the slope, intercept, and correlation coefficient for the straight line which best fit the data. The results for treatments A, B, and C are listed in Table I. Renal clearance plots were prepared by plotting the ampicillin urinary excretion rate for each collection interval *versus* the corresponding plasma ampicillin level at the midpoint of the collection interval. The data for each treatment (all six subjects) was fit to an equation for a straight line passing through the origin:

$$\frac{dU}{dt} = CL_R \cdot C_p \qquad \text{(Eq. 5)}$$

where dU/dt is the ampicillin urinary excretion rate and CL_R represents the ampicillin renal clearance. The slopes of these plots represent ampicillin renal clearance CL_R in liters per hour for treatments A, B, and C and are listed in Table I. The amount of unchanged ampicillin in the urine at time infinity (U_∞) for treatments A, B, and C are 82.04, 104.65, and 122.12 mg, respectively. The values for $\int_0^\infty C_p dt$, the plasma ampicillin AUC from time zero to infinity, were approximated by the values obtained after 24 h. From Table II, AUC values for treatments A, B, and C are 6.43, 7.07, and 7.58 h·mg/L, respectively. The calculated renal clearances are listed in Table I.

Saliva Ampicillin—The values of t_{max}, C_{max}, and AUC for saliva ampicillin are presented in Table III along with the results of paired t tests. In every subject, saliva ampicillin levels were <0.2 μg/mL.

Sarpicillin—Typical sarpicillin plasma levels obtained after oral administration of treatments A, B, and C are illustrated in Fig. 4. The average of the observed values of t_{max}, C_{max}, and AUC of the individual sarpicillin plasma level *versus* time curves are compared in Table IV with the observed t_{max}, C_{max}, and AUC of the average sarpicillin plasma level

Table II—Bioavailability Parameters and Statistics for Plasma Ampicillin After Administration of Sarpicillin

Parameter[a]	Treatment[b] A	B	C
t_{max}[c], h I	0.5	1.5	1.5
II	0.60	1.24	1.43
III	1.08(0.96)	1.25(0.50)	1.46(0.51)
C_{max},[c] (μg/mL) I	2.42	2.85	2.15
II	2.47	2.20	2.25
III	2.65(0.83)	3.38(1.06)	2.65(0.66)
AUC[c], μh · g/mL I	6.44	7.07	7.58
II	6.46	6.79	7.61
III	6.43(0.56)	7.07	7.58(0.86)

[a] I = Values observed from average data. II = Values from predicted points after NONLIN digital computer fit. t_1 max, C_{max}, and AUC were calculated from Eqs. 2, 3, and 4, respectively. III = Average of values observed for individual subject data. [b] Treatment A (buffered tablet), treatment B (soft gelatin capsule), and treatment C (standard gelatin capsule). *SD* in parentheses. [c] Paired t test at $p < 0.05$ indicates no significant difference between treatments.

Table III—Bioavailability Parameters and Statistics for Saliva Ampicillin After Administration of Sarpicillin

Parameter[a]	Treatment[b] A	B	C
t_{max}[c], h I	0.50	1.25	0.75
II	0.46(0.10)	1.04(0.39)	0.81(0.19)
C_{max}[c], μg/mL I	0.20	0.10	0.15
II	0.20(0.09)	0.15(0.05)	0.18(0.12)
AUC[c], h · μg/mL I	0.18	0.16	0.17
II	0.18(0.10)	0.16(0.05)	0.17(0.90)

[a] I = Values observed from average data. II = Average of values observed for individual subject data. [b] Treatment A (buffered tablet), treatment B (soft gelatin capsule), and treatment C (standard gelatin capsule). *SD* in parentheses. [c] Paired t test at $p < 0.05$ indicates a significant difference between treatments A–B and A–C.

data. Paired t tests between treatments for t_{max} are also included in Table IV. In every subject, traces of sarpicillin were found in the urine.

Saliva–Plasma Drug Ratios—Ratios of saliva ampicillin to plasma ampicillin and to plasma sarpicillin for each treatment are presented in Table V. AUC ratios are also listed, and all values are calculated from average data for the six subjects.

DISCUSSION

Kinetic Analysis—*Ampicillin*—Jusko and Lewis (8) used a two-compartment open-body model to describe the disposition kinetics of ampicillin after intravenous administration in humans. After oral administration of ampicillin, absorption and distribution occur simultaneously and could not be distinguished kinetically; a one-compartment open model was sufficient to fit the data (8). Pharmacokinetic analysis of the plasma ampicillin data after oral administration of sarpicillin also fit a one-compartment open model. A first-order input was used to represent intestinal absorption. Since the initial rise of ampicillin plasma levels were slightly delayed, a lag time, L, was incorporated into the mathematical model as seen in Eq. 1. This lag time may be the result of delayed absorption, conversion of sarpicillin to ampicillin, or a combination of both, since some conversion may occur prior to absorption. It would seem that this model is an oversimplification of the true situation considering the lipophilic nature of the prodrug. This is probably the case, but the data were fit very nicely by this model, as seen in Table I. The best fits of the data, as judged by the R-squared values and visual inspection, were obtained using weights of $1/y_{obs}$.

The sigma-minus plots of urine data also show first-order elimination of ampicillin. The slopes of these plots represent the overall elimination rate constants and are in reasonable agreement with those from the plasma data (Table I). Jusko and Lewis found β-phase elimination rate constants for ampicillin of 0.54 and 0.50 h^{-1} after intravenous ampicillin and hetacillin administration, respectively (8). These values are similar to the ampicillin elimination rate constants after sarpicillin administration (Table I). The much larger rate constant for absorption and shorter lag time, clearly indicate that ampicillin appears in the plasma more rapidly from the buffered tablet (treatment A) than from either of the capsules (treatments B and C). The larger D/Vd values for treatments B and C reflect the larger elimination rate constants and longer times to peak levels for these treatments.

Renal clearance, estimated from the slopes of clearance plots, are listed in Table I for the three treatments. The smaller clearance for treatment

Table IV—Bioavailability Parameters and Statistics for Plasma Sarpicillin

Parameter[a]	Treatment[b] A	B	C
t_{max}[c], h I	0.50	0.63	0.75
II	0.38(0.14)	0.92(0.47)	0.71(0.19)
C_{max}, μg/mL I	0.83	0.40	0.70
II	0.85(0.37)	0.72(0.23)	0.80(0.61)
AUC, h · μg/mL I	0.65	0.55	0.75
II	0.68(0.33)	0.57(0.22)	0.78(0.62)

[a] I = Observed values from average data. II = Average of values observed for individual subject data. [b] Treatment A (buffered tablet), treatment B (soft gelatin capsule), and treatment C (standard gelatin capsule). *SD* in parentheses. [c] ANOVA indicates a significant difference among treatments regarding t_{max} at $p < 0.01$. Paired t test at $p < 0.05$ indicates a significant difference for t_{max} between treatments A–B and A–C.

Table V—Saliva–Plasma Drug Ratios of Mean Data for Six Subjects [a]

	Treatment	Ratio						
		0.25 h	0.5 h	0.75 h	1.0 h	1.5 h	2.0 h	AUC
I/II	A	0.229	0.241	0.228	0.286	0.375	—	0.265
I/III	A	0.148	0.083	0.054	0.038	0.017	0.016	0.028
I/II	B	0.067	0.150	0.200	0.303	0.270	1.333	0.281
I/III	B	0.059	0.044	0.043	0.053	0.035	0.020	0.023
I/II	C	0.059	0.155	0.214	0.217	0.233	0.800	0.218
I/III	C	0.333	0.097	0.088	0.063	0.033	0.019	0.022

[a] I = Saliva ampicillin concentration; II = plasma sarpicillin concentration; III = plasma ampicillin concentration.

A appears to be due to the smaller amount of ampicillin eliminated in the urine compared with treatments B and C. Essentially no sarpicillin was detected in the urine, but if it is eliminated by this pathway, the residence time in the bladder would be sufficient for hydrolysis to occur. This would result in artificially high values of dU/dt and renal clearance for ampicillin.

Sarpicillin—As previously indicated, plasma sarpicillin data did not fit the one-compartment model (Eq. 1) to a statistically acceptable degree. As a result, only the simplest pharmacokinetic analysis of this data can be made, which is comparison of the t_{max}, C_{max}, and AUC values. No significant differences were observed for the AUC and C_{max} of sarpicillin plasma levels between treatments, but t_{max} for treatment A is significantly smaller than for treatments B or C, as seen in the paired t test in Table IV. The rate of sarpicillin delivery to plasma is faster for treatment A than B or C, whereas the extent of sarpicillin delivery to plasma is statistically the same for all three treatments.

Saliva–Plasma Drug Analysis—Although in this study sarpicillin saliva levels were found to be <0.2 μg/mL ($CV \leq 10\%$), it is likely that the ampicillin present in saliva originated from plasma sarpicillin which was converted to ampicillin after it reached the saliva. This becomes evident when saliva ampicillin levels are compared with plasma sarpicillin and ampicillin levels. Plasma sarpicillin and saliva ampicillin levels fall to undetectable levels at 3 h, while plasma ampicillin levels are relatively high at that time and become undetectable only after 8 h. For each treatment, the shape of the saliva ampicillin curve more closely resembles that of plasma sarpicillin. The ratios of saliva ampicillin to plasma sarpicillin in Table V are more constant for each treatment than the saliva ampicillin to plasma ampicillin ratios. This is in agreement with the findings of Kjaer and Madsen (13) who suggested that prostatic fluid ampicillin levels in dogs were dependent on the plasma sarpicillin levels. Due to its low pK_a, ampicillin is almost completely ionized in plasma at pH 7.4 while sarpicillin is not. Therefore, ampicillin would be less likely to cross the lipoidal parotid epithelium and enter saliva. In addition, the slight acidity of human saliva (20) creates an unfavorable driving force for pH partitioning of ampicillin from plasma to saliva. Melon and Reginster (21) found that passage of ampicillin into saliva of humans is irregular and very slight, as would be expected. Due to the highly enzymatic nature of saliva, one would expect sarpicillin there to be rapidly converted to ampicillin.

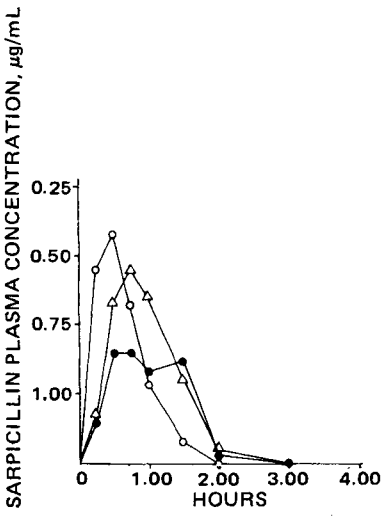


Figure 4—*Sarpicillin plasma concentration obtained after single oral administration of treatments A, buffered tablet (○), B, soft gelatin capsule (●), and C, standard gelatin capsule (△).*

Since saliva ampicillin levels, like plasma sarpicillin, fit the one compartment model poorly, the data were compared by t_{max}, C_{max}, and AUC. As shown by the t_{max} for saliva ampicillin levels in Table III, treatment A delivers ampicillin to saliva more rapidly than treatments B or C, which correlates with the more rapid delivery of sarpicillin to plasma by treatment A. The C_{max} and AUC values for saliva ampicillin levels are not significantly different for the three treatments.

CONCLUSIONS

Based on the time to peak, t_{max}, the rates of delivery of sarpicillin to plasma, ampicillin to plasma, and ampicillin to saliva were greater for the buffered tablet than either the soft gelatin capsule or the standard gelatin capsule. The absorption rate constant obtained from the computer fit of the average plasma ampicillin data (Table I) is statistically greater for the buffered tablet. The t_{max} calculated using k_a and Eq. 2 is also statistically smaller (Table II). However, statistical analysis of t_{max} obtained from the average of values observed graphically for individual subject data indicates no significant differences among or between treatments. The reason for this result is the large t_{max} obtained for subject 4 (3 h) in comparison with the range of values for t_{max} obtained in the rest of the subjects (0.5–1 h). If this subject is eliminated from the statistical analysis as an outlier, the data supports the contention that the plasma ampicillin time to peak is smaller for the buffered tablet than for the two capsule formulations.

Based on AUC values, the extent of delivery of sarpicillin to plasma, ampicillin to plasma, and ampicillin to saliva were statistically the same among treatments. The results of the present investigation suggest that the buffered tablet is a faster and more precise delivery system for sarpicillin than either the liquid formulation in the soft gelatin capsule or the standard gelatin capsule. Reduced excretion of ampicillin following the administration of the sarpicillin buffered tablet may be an indirect indicator of more extensive tissue distribution of sarpicillin and tissue metabolism to inactive metabolites.

Since ampicillin levels were observed in saliva after sarpicillin administration, it is likely that ampicillin levels in lipoidal tissues will be higher than after ampicillin administration. Clinical testing is necessary to determine whether this difference will result in a therapeutic advantage for sarpicillin over ampicillin.

This study is the first human bioavailability comparison of three formulations containing the same amount of sarpicillin base. Further investigation is needed to improve the oral absorption of antibiotics. The rationale for designing new drug delivery systems for sarpicillin and other antibiotics is partially for enhancement of GI absorption, which may potentially increase the tissue concentrations of sarpicillin and consequently maximize therapeutic activity.

REFERENCES

(1) E. L. Flotz, J. W. West, J. H. Breslow, and H. Wallick, *Antimicrob. Agents Chemother.*, **10**, 442 (1970).

(2) L. O. Boreus and B. Jalling, *Pediatr. Clin. North Am.*, **19**, 141 (1972).

(3) J. A. Davis, APhA Symposium on Pharmacokinetics in Disease, Houston, Texas, April 1972.

(4) J. W. Poole, G. Owen, J. Silverio, J. M. Freyhof, and S. B. Rosenman, *Curr. Ther. Res.*, **10**(June), 292 (1968).

(5) B. E. Cabana, L. F. Wilhite, and M. E. Bierwagen, *Antimicrob. Agents Chemother.*, 35 (1969).

(6) L. Magni, G. Ortengren, and S. Wahlqvist, *Scand. J. Lab. Invest.*, **20**, 195 (1967).

(7) C. M. Brown, D. P. Hannan, P. F. Langley, *Toxicol. Appl. Pharmacol.*, **15**(July), 136 (1969).

(8) W. J. Jusko and G. P. Lewis, *J. Pharm. Sci.*, **62**, 69 (1973).
(9) A. Whelton, D. G. Sapir, G. G. Carter, J. Kramer, and W. G. Walker, *J. Pharmacol. Exp. Ther.*, **179**, 419 (1971).
(10) A. T. K. Crockett, R. S. Moore, and A. P. Roberts, *Invest. Urol.*, **5**, 250 (1967).
(11) Disposition and Safety Evaluation Studies of BL-P1761, Bristol Laboratories, Syracuse, N.Y., Jan. 1974.
(12) T. B. Kjaer, P. G. Welling, and P. O. Madsen, *J. Pharm. Sci.*, **66**, 345 (1977).
(13) T. B. Kjaer and P. O. Madsen, *Invest. Urol.*, **14**(July), 57 (1976).
(14) J. A. Bodine, L. J. Strausbaught, and M. A. Sande, *Clin. Pharmacol. Ther.*, **20**, 727 (1976).
(15) M. Pfeffer, Human Study 107, Bristol Laboratories, Syracuse, N.Y., April 1975.
(16) D. C. Grove and W. A. Randall, "Assay Methods of Antibiotics: A Laboratory Manual," Medical Encyclopedia, New York, N.Y., 1955.
(17) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1975.
(18) C. M. Metzler, NONLIN, Technical Report 7292/60/7292/005, The Upjohn Company, Kalamazoo, Mich., 1969.
(19) B. K. Martin, *J. Pharmacol. Chemother.*, **29**, 181 (1967).
(20) F. Rasmussen, *Acta Pharmacol. Toxicol.*, **21**, 11 (1964).
(21) J. Melon and M. Reginster, *Acta Oto-Rhino-Laryngologica Belgica*, **30**, 643 (1976).

ACKNOWLEDGMENTS

This study was supported by a research grant from Bristol Laboratories.

Physicochemical Characterization of Spray-Dried Phenylbutazone Polymorphs

YOSHIHISA MATSUDA ˣ, SACHIYO KAWAGUCHI, HITOMI KOBAYASHI, and JUJIRO NISHIJO

Received September 28, 1982, from the *Kobe Women's College of Pharmacy, Higashinada, Kobe 658, Japan.* Accepted for publication December 17, 1982.

Abstract □ A spray-drying method was applied to the recrystallization of phenylbutazone, and the resulting samples were examined by X-ray powder diffractometry, differential thermal analysis, IR spectrophotometry, scanning electron microscopy, and hot-stage photomicroscopy. Three different crystalline forms (δ, β, and ϵ) could be prepared from methylene chloride solution by varying the drying temperature of sprayed droplets from 120°C to 30°C. Form ϵ, the fifth polymorph of phenylbutazone, was confirmed as a novel crystalline form which could not be prepared by recrystallization techniques. In this spray-drying system the composition of spray-dried samples was shown to be a function of the drying temperature. While the stable form δ was obtained at higher drying temperatures, form ϵ was obtained only under conditions affording a slower evaporation rate of the solvent. The dissolution properties of the pure modifications prepared by recrystallization techniques and the spray-dried samples were evaluated in simulated intestinal fluid. Form ϵ showed excellent *in vitro* availability and much higher solubility than any other of the forms.

Keyphrases □ Phenylbutazone—recrystallized polymorphs, spray-drying technique, physicochemical characterization □ Spray-drying—recrystallized polymorphs of phenylbutazone, physicochemical characterization □ Recrystallization—polymorphs of phenylbutazone, spray-drying technique, physicochemical characterization

The physicochemical properties of solid drug substances are of considerable importance in preformulation studies, because they are related to both the production of dosage forms and bioavailability. The nature of the crystalline forms affects bioavailability through the effect of crystal properties on dissolution rate. In a particular polymorphic form, many solids may be prepared *via* appropriate modification of the conditions of crystallization. Some important factors relating to the resulting crystalline forms when obtaining polymorphs by recrystallization techniques are the nature of solvent (its polarity and solvent power), temperature, and rate of cooling. The latter two factors can take part in the crystallization velocity. Although precise control of the recrystallization velocity is difficult for ordinary recrystallization techniques, a spray-drying method may enable one to produce different crystallization velocities by varying the drying conditions of the sprayed droplets.

While several papers dealing with the polymorphism of spray-dried drug substances have been published (1–5), little information is available on the relationship between the operating factors and the resulting crystalline forms. An interesting polymorphism of phenylbutazone was found using a spray-drying method (6). This paper describes a further investigation to provide basic physicochemical information on the polymorphic forms.

BACKGROUND

There have been several reports describing the polymorphism of phenylbutazone, including our previous communication (Table I). Matsunaga *et al.* (7) found that phenylbutazone gave three polymorphs, *i.e.*, forms I, II, and III, among which the former two polymorphs (available commercially) were considered to be a stable form and one of the metastable forms, respectively. The mutual transformation among them by heating or through grinding and compression has been investigated. Ibrahim *et al.* (8) independently reporting on the polymorphism and feasibility of crystalline structural changes under tableting conditions, found the presence of four forms (I, II, III, and IV). Müller (9) showed later that forms I and II were pseudopolymorphs resulting from solvation. This was also confirmed by our differential thermal analysis–thermogravimetry analysis (DTA–TG). While Müller suggested the existence of a fourth polymorph (form γ) other than forms α, β, and δ (which had been already identified), he could not isolate it, despite describing its thermogram. In the same year Chauvet *et al.* (10) reported the thermal behavior of three polymorphs, *i.e.*, forms I, II, and III, obtained by different methods, all of which were identical to those already found. They considered that form II was identical to that reported by Matsunaga; however, based on the results of thermomicroscopy and thermal analysis, we estimated that the form II should actually be identical to the form γ designated by Müller (9). In a previous publication, it was shown that a fifth crystalline form (form ϵ) is formed together with forms β and δ in a spray-drying system. In this system forms α and γ

0022-3549/84/0200-0173$01.00/0